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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/730,617	12/05/2000	Catherine Burgess	15966-609 (CURA-109)	7404

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Ivor R. Elrifi, Ph.D.
Mintz, Levin, Cohn, Ferris,
Glovsky and Popeo, P.C.
One Financial Center
Boston, MA 02111

EXAMINER	
WEGERT, SANDRA L	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/18/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/730,617	BURGESS ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 56-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 56-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-3 and 56-68* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The examiner in charge of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Sandra Wegert in Group Art Unit 1647.

DETAILED ACTION

The Preliminary Amendment of 6/13/02 (Paper 14) was received *after* mailing of the last Office Action (6/27/02, Paper 13). Upon further consideration, the last Office Action is hereby VACATED. A new Office Action follows:

Status of Application, Amendments, and/or Claims

The Information Disclosure Statement, received 31 August 2001, has been entered as Paper 9. Applicant's election without traverse of Invention I, (claims 1-4) in Paper No. 12 (18 March 2002) is acknowledged. In addition, Applicant elected the following: The polypeptide of SEQ ID NO: 4. Claims 4-55 have been cancelled by the Applicant in Paper 14. Claims 56-68 were added and read on the elected Invention.

Claims 1-3 and 56-68 are under examination in the current application.

Informalities

Specification

The disclosure is objected to because of the following informalities:

Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "HUMAN NEUROMEDIN PROTEIN".

Appropriate correction is required.

URL's

The disclosure is objected to because it contains browser-executable code. This occurs, for example, on page 11, lines 17 and 20, for example. All URL's should be removed from the Specification. Applicant may refer to web sites by non-executable name only. See MPEP § 608.01 (p).

Appropriate correction is required.

Claim Rejections/Objections

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

The following is a quotation of 35 U.S.C. 101:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 56-68 are rejected under 35 U.S.C. 101 because the claimed invention lacks a credible, specific and substantial asserted utility or a well-established utility.

The claims are directed to the peptide and variants of SEQ ID NO: 4.

No well-established utility exists for newly isolated complex biological molecules. However, the specification asserts the following as credible, specific and substantial patentable utilities for the claimed polypeptides:

1) to probe DNA databases to search for related sequences,

2) in diagnosing a dysfunction associated with the polypeptide of SEQ ID NO: 4,

3) for use in *in situ* assays of gene or chromosome localization,

4) to detect pharmacogenomically-relevant polymorphisms,

5) in the creation of transgenic animals,

6) for gene therapy, and

7) in tissue typing.

Each of these shall be addressed in turn.

1) to probe DNA databases to search for related sequences. This asserted utility is credible but not substantial or specific. Probes can be designed from any polynucleotide encoding a polypeptide. Further, the specification does not disclose specific cDNA, DNA, or RNA targets. Since this asserted utility is not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

2) in diagnosing a dysfunction associated with the polypeptide of SEQ ID NO: 4. Similarly, this asserted utility is credible and specific, however, it is not substantial. The specification does not disclose any function, nor any dysfunction, associated with altered levels

or forms of the polypeptide encoded by SEQ ID NO: 4. Significant further experimentation would be required of the skilled artisan to identify a dysfunction or disease associated with the claimed polypeptide. There is no disclosure, for example, of any symptoms associated with such a disease or dysfunction of the polypeptide. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

3) for use in in situ assays of gene or chromosome localization. This asserted utility is credible but is neither substantial nor specific. Applicant refers to the use of a hybridization probe to localize genes or gene fragments within a chromosome. However, probes can be designed from any polynucleotide sequence, and thus the asserted utility is not specific. Further, the specification does not disclose specific cDNA, DNA, or RNA targets. Since this asserted utility is not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) to detect pharmacogenomically-relevant polymorphisms. This asserted utility may be credible, however it is neither specific nor substantial. Generally, the well-known polymorphisms occur in metabolic enzymes (e.g. the liver P450's or the dehydrogenases), and are very well characterized physiologically and within populations. Applicants have not demonstrated the function of the polypeptide, much less clinically-relevant polymorphisms in the genes encoding the claimed polypeptide. Thus, the asserted utility is not substantial. Finally, many unrelated sequences can be polymorphic, generally. Thus, the asserted utility is not specific.

5) In the creation of transgenic animals. This asserted utility is credible but not specific or substantial. The specification does not disclose diseases associated with a mutated, deleted, or translocated gene of the present invention. Significant further experimentation would be required of the skilled artisan to identify such a disease. The specification discloses nothing about whether the claimed gene will be "knocked in" or "knocked out" or what specific tissues and cells are being targeted. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

6) for gene therapy. This asserted utility is credible but not specific or substantial. Such can be performed for any polynucleotide. Further, the specification does not disclose diseases associated with mutated, deleted, or translocated genes encoding the polypeptide of SEQ ID NO: 4. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease and to determine the route of administration of the gene, as well as quantity and duration of treatment. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

7) *in tissue typing.* This asserted utility is credible but not substantial or specific. Such assays can be performed with any polypeptide encoded by a polynucleotide; thus the asserted utility is not specific. Furthermore, the specification discloses a wide range of tissues that express the polypeptide of SEQ ID NO: 4. Applicants have demonstrated that the polypeptide of SEQ ID NO: 4 in the instant application is expressed in various tissues, including the adrenal gland, thyroid gland, brain neurons, brain glia, mammary glands, and several human cancer cell lines and primary cultures. Applicant implies that this expression supports a useful function of the polynucleotide encoding SEQ ID NO: 4. However, patentable utility of tissue typing for the

polynucleotide encoding the claimed polypeptide is not substantial because one skilled in the art would not readily use the nucleotide sequences for tissue-typing in a real world sense as the protein is not specific to one tissue and is not associated with any disease or disorder. This asserted utility is also not specific because numerous unrelated nucleotide sequences would also show a similar tissue typing pattern. In addition, evidence of mere expression in a tissue is not tantamount to a showing of a role for the polynucleotide of the present invention. It is not clear if expression of the polynucleotide of the present Invention is correlated with a specific change in physiology, for example, or with a disease state. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Claims 1-4 and 56-68 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1-4 and 56-68 are directed to the polypeptide of SEQ ID NO: 4. The claims also recite variants of the polypeptide of SEQ ID NO: 4.

The specification teaches the polypeptide of SEQ ID NO: 4. However, the specification does not teach functional or structural characteristics of the polypeptides recited in the claims.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is

insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologues must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Examples from the peptide hormone art demonstrate polypeptides with high homology having a wide-variety of functions in organisms. Even closely-related family members sometimes work very differently and have different specific functions in the organism. Kopchick, et al (1994, US Patent 5,350,836) showed that small modifications at a single residue

changed Bovine Growth Hormone from an agonist to an antagonist. Likewise, PTH and PTHrP are two structurally closely related proteins, which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). These examples illustrate that one skilled in the art would not know the utility and function of the claimed polypeptide, even if it were classified as a receptor ligand in the neuromedin family.

Based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to make biologically active peptides of SEQ ID NO: 4 without resorting to undue experimentation to determine what the specific biological activities of the polypeptides are.

The specification does not teach the skilled artisan how to use the claimed polypeptides for *any* purpose. For example, there is no disclosure of particular disease states correlating to an alteration in levels or forms of the polypeptide such that the polypeptides could be used as a diagnostic tool. There are no experiments using the polypeptide as cytokine or hormone for cells or organisms, for example. The skilled artisan is not provided with sufficient guidance to use the claimed polypeptide for any purpose.

Due to the large quantity of experimentation necessary to determine an activity or property of the disclosed polypeptide such that it can be determined how to use the claimed polypeptide and to screen for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity and the unpredictability of the effects of variation and

mutation on protein structure and function, as well as the breadth of the claim which fail to recite particular biological activities - undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Furthermore, regarding Claims 2, 3, 56-59 and 61-66, the specification does not enable variants of SEQ ID NO: 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims.

The claims are directed to the polypeptide and variants of SEQ ID NO: 4. Claims 2, 3, 56-59 and 61-66 read on peptides and variants that are at least 90% identical to SEQ ID NO: 4. The scope of the patent protection sought by the Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons:

The Instant Application does not reasonably provide enablement for various protein forms of SEQ ID NO: 4, wherein the protein's sequence is at least 90% identical to the amino acid sequence of the polypeptide and variants of SEQ ID NO: 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention or further variants of the claimed Invention.

Claims 56-58, 62-64 and 66 are directed to polypeptides that are at least 90% identical to that of SEQ ID NO: 4. The specification discloses a neuromedin-like polypeptide having an amino acid sequence shown in SEQ ID NO: 4. The specification is not enabled for the full scope of the protein, wherein the encoded amino acid sequence is at least 90% identical to SEQ ID NO: 4, with the assurance that enabled proteins can be made without undue experimentation and with the assurance that they would have the desired properties. There are no examples of what specific polypeptides fall within the range of those that would be 90% identical. Neither is it clear if this percent identity need be over a contiguous region or a specific portion of the protein.

Similarly, Claims 2, 3, 61 and 63-66 read on variants of SEQ ID NO: 4. However, the specific activities of the claimed proteins are not disclosed. Nor are there disclosed assays to test for these activities. There is no discussion or working examples, disclosed in the instant case, as to what amino acids are necessary to maintain the functional characteristics of the polypeptides as claimed. Claims 2, 3, 61 and 63-66 encompass undefined variants of SEQ ID NO: 4. However, as discussed above, it is not predictable as to which amino acids are necessary to maintain the functional characteristics of a protein.

Furthermore, the specification does not reasonably provide enablement for use of the polypeptide or polynucleotide *allelic variants* as recited in claims 59 and 65. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Applicants have not identified allelic variants of the polypeptide of SEQ ID NO: 4, nor precisely localized it to a particular locus of a chromosome. Claims 59 and 65 encompass undefined variants of SEQ ID NO: 4, without precise recitations of function that can be applied to allelic

variants. Furthermore, as discussed above, it is not predictable as to which variations are tolerated while still maintaining the functional characteristics of a protein.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim.

Due to the large quantity of experimentation required to determine how to use variants of SEQ ID NO: 4, the lack of direction or guidance in the specification regarding specific activity of the polypeptide encoded by SEQ ID NO: 4, the lack of working examples to variants of SEQ ID NO: 4, the state of the art showing the unpredictability of function based on structure, and the breadth of the claim which embrace innumerable variants of the polypeptides of SEQ ID NO: 4 - undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

35 USC § 112, first paragraph – written description.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> ***The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.***

Claims 59 and 65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 59 and 65 are directed to allelic variants of SEQ ID NO: 4. The claims refer to the polypeptide of SEQ ID NO: 4 and its allelic variants of a polynucleotide of SEQ ID NO: 3.

The specification teaches a polypeptide (SEQ ID NO: 4) and a polynucleotide (SEQ ID NO: 3). However, the specification does not teach functional or structural characteristics of *allelic variants* of the disclosed polynucleotides. The description of one polynucleotide encoding a polypeptide (SEQ ID NO: 3) is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement

that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 3 and a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO: 4, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion: Claims 1-3 and 56-68 are rejected for the reasons listed above.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. The examiner can normally be reached Monday - Friday from 9:30 AM to 6:00 PM (Eastern Time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SLW
9/14/02

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER